

University of Groningen

Vilazodone does not inhibit sexual behavior in male rats in contrast to paroxetine

Oosting, Ronald S.; Chan, Johnny S W; Olivier, Berend; Banerjee, Pradeep

Published in:
Neuropharmacology

DOI:
[10.1016/j.neuropharm.2016.03.045](https://doi.org/10.1016/j.neuropharm.2016.03.045)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Oosting, R. S., Chan, J. S. W., Olivier, B., & Banerjee, P. (2016). Vilazodone does not inhibit sexual behavior in male rats in contrast to paroxetine: A role for 5-HT_{1A} receptors? *Neuropharmacology*, 107, 271-277. <https://doi.org/10.1016/j.neuropharm.2016.03.045>

Copyright

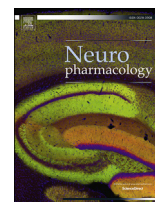
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Vilazodone does not inhibit sexual behavior in male rats in contrast to paroxetine: A role for 5-HT_{1A} receptors?



Ronald S. Oosting^{a, *}, Johnny S.W. Chan^a, Berend Olivier^{a, b, c}, Pradeep Banerjee^d

^a Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands

^b Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

^c Groningen Institute for Evolutionary Life Sciences (GELIFES), Rijksuniversiteit Groningen, The Netherlands

^d Forest Research Institute (an Allergan affiliate), 1900 Plaza Five, Jersey City, NJ 07311, USA

ARTICLE INFO

Article history:

Received 7 December 2015

Received in revised form

18 March 2016

Accepted 25 March 2016

Available online 31 March 2016

Keywords:

Preclinical

Antidepressant

Serotonin receptor

Partial agonism

ABSTRACT

Vilazodone (VLZ) is a selective serotonin reuptake inhibitor (SSRI) and 5-HT_{1A} receptor partial agonist approved for the treatment of major depressive disorder in adults. In preclinical studies, VLZ had significantly lower sexual side effects than SSRIs and reduced serotonin transporter (SERT) levels in forebrain regions. In the current study, once-daily paroxetine (PAR, 10 mg/kg), VLZ (10 mg/kg), PAR + buspirone (BUS, 3 mg/kg; a 5-HT_{1A} partial agonist), or vehicle (VEH) was administered to male rats for 2 weeks then switched for 7 days (eg, PAR switched to VLZ, PAR + BUS, or VEH). Sexual behavior (eg, ejaculation frequency and latency) was evaluated 1-hr postdose on days 1, 7, 14, and 21. After 2 weeks, treatment with PAR but not VLZ resulted in a significant decrease in sexual behavior. In a 30-min test, the range of ejaculation frequency was 3.08–3.5 with VLZ and 1.00–1.92 with PAR ($P < 0.05$ vs VEH). After switching from PAR to VEH, PAR + BUS, or VEH, sexual behaviors were normalized to control levels. In contrast, the switch from VLZ to PAR resulted in reduced sexual behaviors. This preclinical study showed that unlike PAR, an SSRI with no 5-HT_{1A} receptor activity, initial treatment with VLZ did not result in sexual side effects at therapeutically relevant doses. Results in male rats switched from PAR to VLZ or PAR + BUS strongly suggest that activation of 5-HT_{1A} receptors may mitigate the sexual side effects associated with conventional SSRIs.

© 2016 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Major depressive disorder (MDD) is one of the most common mental disorders worldwide (Bromet et al., 2011), and antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are among the most frequently prescribed drugs (Lindsley, 2012). The clinical efficacy can be limited, however, due to adverse sexual side effects that may affect up to 60% of patients treated with SSRIs (Kennedy and Rizvi, 2009). These SSRI-induced sexual side effects can lead to treatment noncompliance and discontinuation (Ashton et al., 2005), which can lower patient quality of life (Hu et al., 2004) and increase the risk of relapse and recurrence of MDD (Clayton and Montejo, 2006). Therefore, understanding the neurobiology

underlying SSRI-induced sexual dysfunction and identifying treatment options with a lower risk of adverse impact on sexual function may help to optimize the management of MDD and improve patient outcomes.

Strategies used to mitigate the adverse sexual side effects of SSRIs include lowering dosage, switching class of antidepressant medication (eg, norepinephrine-dopamine reuptake inhibitor), or adding concomitant medications such as a phosphodiesterase inhibitor type 5 (PDE5; eg, sildenafil) or 5-HT_{1A} receptor partial agonists (Rizvi and Kennedy, 2013).

Preclinical studies and clinical evidence support a role for 5-HT_{1A} receptors in modulating sexual behavior. Buspirone and its major active metabolite, 6-OH-buspirone, act as partial agonists at presynaptic 5-HT_{1A} receptors in the raphe nuclei (higher affinity) and at postsynaptic 5-HT_{1A} receptors throughout the brain (lower affinity) (Wong et al., 2007). Studies in male rats have shown that 5-HT_{1A} receptor agonists (8-OH-DPAT, FG-5893, flesinoxan), as well as the partial agonist buspirone, have a facilitating effect on sexual behavior (Bijlsma et al., 2014; Chan et al., 2008). In contrast, the 5-

* Corresponding author. Department of Psychopharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands.

E-mail address: R.S.Oosting@uu.nl (R.S. Oosting).

Abbreviations

ANOVA	analysis of variance
BUS	buspirone
DA	dopamine
FDA	US Food and Drug Administration
MDD	major depressive disorder
MPOA	medial preoptic area
PAR	paroxetine
PDE5	phosphodiesterase inhibitor type 5
PO	orally administered
SEM	standard error of the mean
SER	sertraline
SERT	serotonin transporter
SSRI	selective serotonin reuptake inhibitor
VLZ	vilazodone
VEH	vehicle

HT_{1A} receptor antagonist WAY-100635 was found to inhibit sexual behavior when coadministered with the SSRIs citalopram and paroxetine (Olivier et al., 2011) and when administered to serotonin transporter (5-HT_T) knockout rats (Chan et al., 2011). In a clinical study of depressed patients, addition of the 5-HT_{1A} receptor partial agonist buspirone improved sexual function in patients who had been experiencing sexual dysfunction while taking an SSRI (ie, paroxetine or citalopram) (Landen et al., 1999).

Vilazodone is an SSRI and 5-HT_{1A} receptor partial agonist approved by the Food and Drug Administration (FDA) for the treatment of MDD in adults. In clinical trials, vilazodone was associated with a low adverse impact on sexual function relative to the high prevalence of sexual dysfunction that was present in the patients at baseline (Clayton et al., 2013a). In preclinical studies, acute treatment with vilazodone showed dose-dependent occupancy of 5-HT_T and 5-HT_{1A} receptors in the rat cortex and hippocampus, with systemic administration of 10 mg/kg vilazodone producing ~90–100% occupancy at serotonin transporter (SERT) and 5-HT_{1A} receptors and resulting in a 2-fold increase in extracellular 5-HT in the rat frontal cortex (Hughes et al., 2005). Results from another preclinical study showed that treatment with vilazodone (acute [1 d], subchronic [7 d], or chronic [14 d]) was not associated with sexual dysfunction in a rat sexual behavior model (Oosting et al., 2016). Similar treatments with the SSRIs citalopram and paroxetine were associated with sexual dysfunction, with vilazodone causing a marked decrease in 5-HT_{1A} receptor levels in the cortex and hippocampus and the SSRIs causing increased receptor levels in similar regions.

The current study was conducted to investigate whether switching treatments from (chronically administered) paroxetine, an SSRI known to cause sexual dysfunction in rats, to a treatment that includes both SSRI and 5-HT_{1A} receptor partial agonism (ie, vilazodone or paroxetine + buspirone coadministration) normalizes rat sexual behaviors. The doses of drugs that were administered to rats in this study (vilazodone, paroxetine, buspirone) were selected based on SERT and 5-HT receptor occupancy data (Hughes et al., 2005) and because they fall within the dose ranges for animal paradigms used to screen for antidepressant and anxiolytic activity (Adamec et al., 2004; Page et al., 2002).

2. Experimental procedures

2.1. Animals

Male (300–400 g) and female (200–300 g) Wistar rats (Charles River Laboratories, FR) were group housed (4 per cage) with food and water ad libitum. All animal cages were stored in the same room maintained at 21 °C and 55% humidity. Rats were habituated for 1 week to reversed light/dark schedule (lights off 7:00; lights on 19:00). All experiments were reviewed and approved by Utrecht University's animal welfare committee (DEC), in accordance with the European Communities Council Directive of 24 November 1986.

2.2. Drug administrations

Vilazodone hydrochloride was obtained in powder form from Forest Laboratories, Inc. (an Allergan affiliate). Paroxetine hydrochloride and buspirone hydrochloride tablets (Sandoz, France) were purchased from a local pharmacy in generic form. All drugs were dissolved or suspended in vehicle (1% methylcellulose and water) and orally administered (PO) between 9:00 and 15:00 (non-test days) or 1 h before testing. Doses were 10 mg/kg for vilazodone and paroxetine; 3 mg/kg buspirone was co-administered with 10 mg/kg paroxetine.

2.3. Sexual behavior test

The sexual behavior test was performed as previously described (Chan et al., 2010). All assessments were performed in the dark phase of the light/dark-cycle under dim red light conditions.

2.4. Sexual training and selection of male rats

144 male rats were trained (30 min) once weekly for 4 consecutive weeks with an estrus female that was located in an observation cage behind a clear Plexiglas front. At 36 h before the test, the female received a subcutaneous injection of 50 µg estradiol-benzoate dissolved in sesame oil to induce receptivity. Males that exhibited 2–3 ejaculations during the final three 30-min training sessions were classified as normal-performers (Pattij et al., 2005) and were included in the drug testing studies (n = 84).

2.5. Experimental design and testing

Male normal-performers were divided into 7 treatment groups (n = 8 per group) that consisted of 2 distinct successive pharmacological treatments (exception was vehicle-to-vehicle group). The experimental design is shown in Fig. 1. Rats received the first treatment for 14 d and were switched to the second treatment for an additional 7 d.

Male rats were placed in an observation cage (30 × 40 × 60 cm) with an estrus female on Day 1 (acute), Day 8 (subchronic), Day 15 (chronic), and Day 22 (7 d after switch) to score sexual behavior. Evaluations included the frequencies of mounts (no vaginal penetration) and intromissions (vaginal penetration) in the first ejaculation series, latency to the first ejaculation (time between the first mount or intromission to first ejaculation), and ejaculation frequency for the duration of the 30-min test. Copulatory efficiency was defined as: # intromissions/(# intromissions + # mounts) × 100%. All measurements and scoring were performed using Observer[®] 5.0 (Noldus, Wageningen, The Netherlands).

2.6. Statistical analysis

Data for each sexual behavior test day (acute, subchronic,

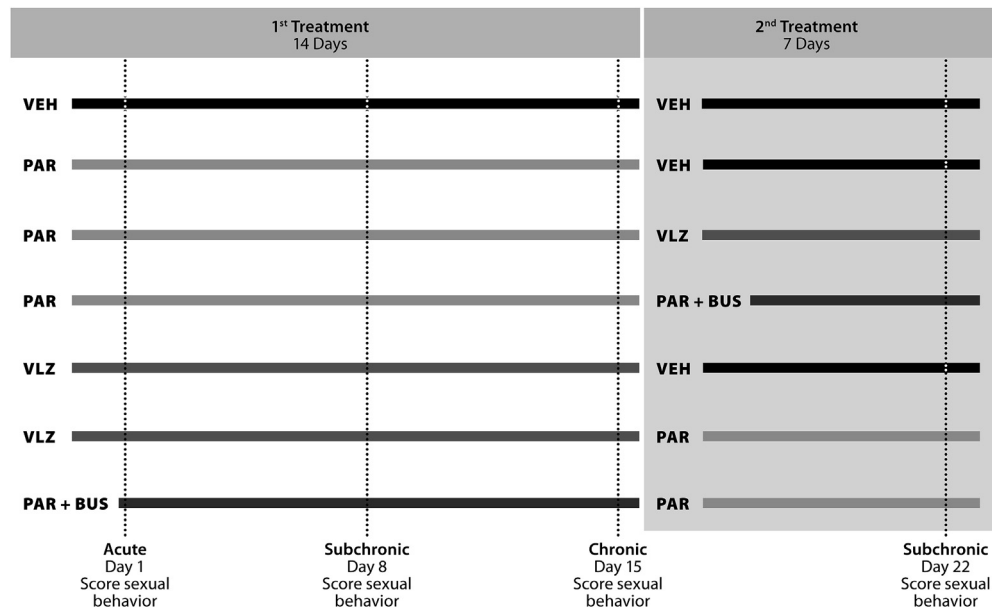


Fig. 1. Experimental Design. BUS indicates buspirone; PAR, paroxetine; VEH, vehicle; VLZ, vilazodone. N = 8/group.

chronic, and post-switch) were analyzed using a one-way analysis of variance (ANOVA) to determine the effects of treatment on a particular test day. Each one-way ANOVA included groups that received the same pre-switch treatment (paroxetine, vilazodone, and paroxetine + buspirone) and the vehicle group. When the ANOVA indicated a significant treatment effect, Bonferroni post hoc corrections were performed to investigate differences between the treatments.

Time-by-treatment interactions were analyzed using repeated measure ANOVAs with Greenhouse-Geisser correction. Time was based on the 4 test days representing acute (Day 1), subchronic (Day 8), chronic (Day 15), and post-switch treatment (Day 22); treatment groups were based on pre-switch assignments (eg, paroxetine with a switch to vehicle, vilazodone, or paroxetine + buspirone) as well as the vehicle control group. All significance testing was 2-sided at the $P \leq 0.05$ level. All data are represented as the mean and standard error of the mean (SEM).

3. Results

Representative tracings of individual rat sexual behaviors (mount, intromission, and ejaculations) during the 30-min sex tests following subchronic (7 d), chronic (14 d), and 7 d post-switch are shown in Supplemental Fig. 1.

3.1. Pre-switch treatments

Ejaculation frequency, first series ejaculation latency, and first series copulatory efficiency following the acute, subchronic, and chronic treatments are shown in Table 1. Following the acute treatments with vehicle, paroxetine, paroxetine + buspirone, or vilazodone there were no significant differences of the sexual behaviors (Table 1, Figs. 2 and 3). However, subchronic and chronic paroxetine treatments resulted in reduced ejaculation frequency, increased latency to first ejaculation, and reduced copulatory efficiency. The paroxetine + buspirone treatment impaired ejaculation frequency (chronic) and copulatory efficiency (subchronic and chronic), but had no effect on latency to first ejaculation. Vilazodone treatment did not result in any differences in sexual behaviors

Table 1

Sexual behaviors following acute, subchronic, and chronic treatments.

Treatment	Acute	Subchronic	Chronic
Ejaculation frequency, #			
VEH	2.8 ± 0.4	3.1 ± 0.2	3.2 ± 0.2
PAR	2.6 ± 0.3	0.8 ± 0.3 ^{a,b,c}	1.5 ± 0.3 ^{a,b,c}
PAR + BUS	2.6 ± 0.3	2.3 ± 0.4	2.0 ± 0.3 ^{a,c}
VLZ	3.0 ± 0.2	3.6 ± 0.2	3.3 ± 0.2
First series ejaculation latency, sec			
VEH	367 ± 136	333 ± 59	269 ± 62
PAR	350 ± 99	1329 ± 531 ^{a,b,c}	910 ± 188 ^{a,c}
PAR + BUS	281 ± 66	549 ± 189	522 ± 138
VLZ	280 ± 63	183 ± 31	245 ± 57
First series copulatory efficiency, %			
VEH	60 ± 7.7	58 ± 2.9	62 ± 3.9
PAR	49 ± 7.2	21 ± 2.3 ^{a,b,c}	33 ± 3.2 ^{a,b,c}
PAR + BUS	51 ± 6.9	38 ± 8 ^a	38 ± 5.0 ^{a,c}
VLZ	57 ± 4.9	70 ± 4	62 ± 3.9

All data are shown as the mean ± standard error of the mean for all animals in each pre-switch treatment group: VEH (n = 8); PAR (n = 24); PAR + BUS (n = 8); VLZ (n = 16). Lower values indicate greater impairment for ejaculation frequency and copulatory efficiency; higher values indicate greater impairment for ejaculation latency.

Abbreviations: #, number per 30 min; VEH, vehicle (n = 10); PAR, paroxetine (10 mg/kg; n = 34); BUS, buspirone (3 mg/kg; n = 12); VLZ, vilazodone (10 mg/kg; n = 24); sec, seconds.

^a $P \leq .05$ versus vehicle.

^b $P \leq .05$ versus paroxetine + buspirone.

^c $P \leq .05$ versus vilazodone.

from vehicle treatment. Bonferroni post hoc corrections for comparisons between treatment groups on each test day are described below and shown in Table 1.

3.1.1. Comparisons with paroxetine

Comparisons between treatment groups indicated that paroxetine-treated rats had worse performance on sexual behavior parameters than the other groups (Table 1, Figs. 2 and 3). Rats in the paroxetine group had reduced ejaculation frequency following subchronic and chronic treatment (both time points, $P \leq 0.001$ vs all other groups), increased ejaculation latency following subchronic treatment ($P \leq 0.001$ vs all other groups) and chronic

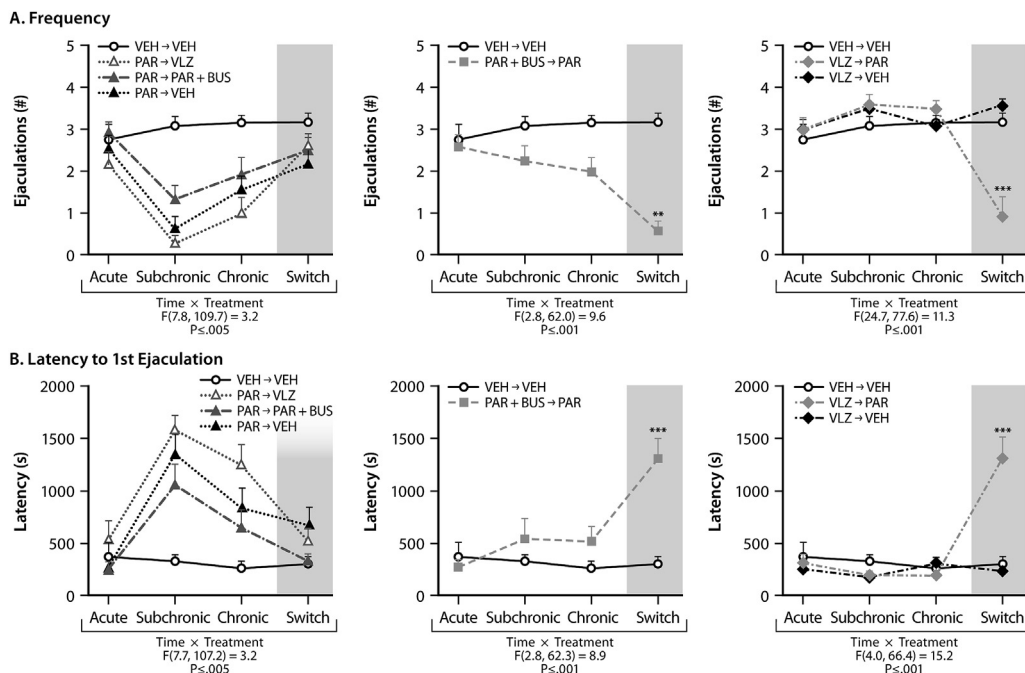


Fig. 2. Ejaculatory Behavior. Effects of paroxetine (10 mg/kg), vilazodone (10 mg/kg), and paroxetine + buspirone (10 and 3 mg/kg, respectively) on (A) ejaculation frequency during the 30-min sex tests and (B) latency to first ejaculation in male Wistar rats ($n = 8/\text{drug/dose}$) conducted after acute (Day 1), subchronic (Day 8), and chronic (Day 15) treatment and after switching treatments for 1 week (Day 22). $^{***}P \leq 0.01$, $^{***}P \leq 0.001$ versus with VEH–VEH based on a one-way ANOVA for the post-switch assessments. Time-by-treatment interactions were analyzed using repeated measure ANOVAs with Greenhouse–Geisser correction. Abbreviations: ANOVA, analysis of variance; BUS indicates buspirone; PAR, paroxetine; VEH, vehicle; VLZ, vilazodone.

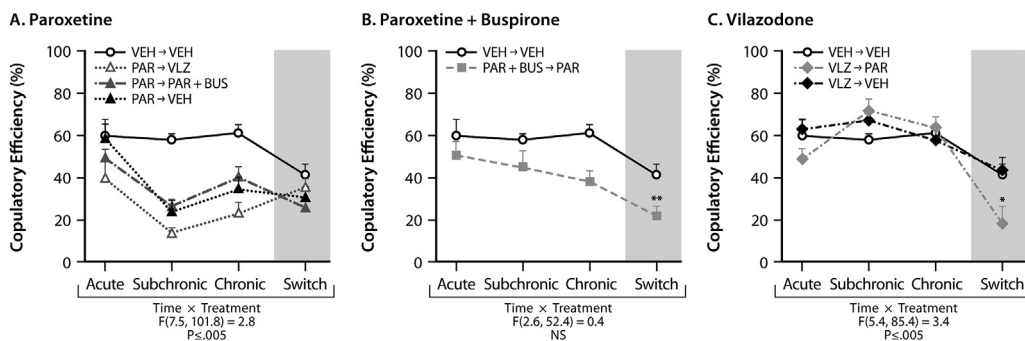


Fig. 3. Copulatory Efficiency. Effects of (A) paroxetine (10 mg/kg), (B) vilazodone (10 mg/kg), and (C) paroxetine + buspirone (10 and 3 mg/kg, respectively) on copulatory efficiency in male Wistar rats ($n = 8/\text{drug/dose}$) conducted after acute (Day 1), subchronic (Day 8), and chronic (Day 15) treatment and after switching treatments for 1 week (Day 22). $^{*}P \leq 0.05$, $^{**}P \leq 0.01$ compared with VEH–VEH based on a one-way ANOVA for the post-switch assessments. Time-by-treatment interactions were analyzed using repeated measure ANOVAs with Greenhouse–Geisser correction. Abbreviations: ANOVA, analysis of variance; BUS indicates buspirone; NS, not significant; PAR, paroxetine; VEH, vehicle; VLZ, vilazodone.

treatment ($P \leq 0.001$ vs vehicle; $P \leq 0.001$ vs vilazodone), reduced copulatory efficiency after subchronic treatment ($P \leq 0.001$ vs vehicle and vilazodone; $P \leq 0.05$ vs paroxetine + buspirone) and chronic treatment ($P \leq 0.001$ vs vehicle and vilazodone; $P \leq 0.01$ vs paroxetine + buspirone).

3.1.2. Comparisons with paroxetine + buspirone

Paroxetine + buspirone-treated rats had reduced ejaculation frequency following chronic (but not subchronic) treatment ($P \leq 0.05$ vs vehicle; $P \leq 0.01$ vs vilazodone; Table 1, Fig. 2A), no changes in ejaculation latency (Table 1, Fig. 2B), and reduced copulatory efficiency following subchronic treatment ($P \leq 0.001$ vs vehicle and vilazodone) and chronic treatment ($P \leq 0.05$ vs vehicle, $P \leq 0.01$ vs vilazodone) (Table 1, Fig. 3B).

3.1.3. Comparisons with vilazodone

Unlike the paroxetine- and paroxetine + buspirone-treated rats, vilazodone-treated rats did not exhibit impairments in any of the sexual behaviors relative to the vehicle-treated rats (Table 1, Figs. 2 and 3).

Notably, the significant differences between vilazodone and paroxetine + buspirone for ejaculation frequency and copulatory efficiency (Table 1) suggested that these treatments did not have equivalent effects on the sexual behaviors.

3.2. Post-switch treatments

3.2.1. From paroxetine to paroxetine + buspirone or vilazodone

Paroxetine-treated rats that had previously exhibited ejaculatory and copulatory sexual dysfunction returned to control (ie,

vehicle-vehicle) levels following 7 d treatment with vehicle, paroxetine + buspirone, or vilazodone (Figs. 2 and 3A).

3.2.2. From paroxetine + buspirone to paroxetine

Rats that were switched from paroxetine + buspirone to paroxetine only treatment exhibited decreased ejaculation frequency, increased latency to first ejaculation, and reduced copulatory efficiency compared with vehicle (all $P \leq 0.01$; Fig. 2A, B and 3B).

3.2.3. From vilazodone to paroxetine

There were no differences in sexual behaviors of vilazodone-treated rats that were switched to vehicle compared with vehicle-vehicle controls (Figs. 2 and 3C). Vilazodone-treated rats that were switched to paroxetine exhibited decreased ejaculation frequency, increased latency to first ejaculation, and decreased copulatory efficiency compared with vehicle-vehicle controls (all $P \leq 0.05$; Figs. 2A, B and 3C).

3.2.4. Time-by-treatment interactions

All time-by-treatment interactions were significant ($P \leq 0.005$) except for the model that analyzed copulatory efficiency in the group that switched from paroxetine + buspirone to paroxetine alone and the vehicle control group (Fig. 3B).

4. Discussion

The current study investigated the role of combined 5-HT_T inhibition and 5-HT_{1A} receptor partial agonism on male rat sexual behaviors. In general, the results suggest that SSRI-induced sexual dysfunction was normalized when treatments included both SSRI and partial 5-HT_{1A} receptor agonism (ie, vilazodone or paroxetine + buspirone).

SSRI treatment can cause sexual dysfunction in all 3 phases of the human sexual response cycle, which includes desire, arousal, and orgasm (Serretti and Chiesa, 2009; Waldinger et al., 2001). Male rats exhibit a similar sexual response cycle that includes the behaviors of approaching and sniffing (precopulatory), repeated intromissions and mounting (copulatory), and ejaculation (Snoeren et al., 2014). In the current study, male rat sexual behavior was not affected by acute treatment with paroxetine alone, as was expected from previous studies that showed no sexual side effects after acute SSRI administration in rats (Olivier et al., 2011; Waldinger et al., 2002) or humans (Waldinger et al., 2001). The most robust inhibitory effects were seen after subchronic paroxetine treatment, with some recovery after longer (chronic) exposure. The reason for this trend is not clear, but we have occasionally observed a tendency towards recovery in previous studies with similar treatment paradigms that also used paroxetine as the reference compound (Bijlsma et al., 2014; Chan et al., 2008; Olivier et al., 2011).

Based on previous evidence showing that administration of 5-HT_{1A} receptor agonists and partial agonists enhanced male sexual behaviors in rodents (Arnone et al., 1995; De Jong et al., 2005; Snoeren et al., 2014) and improved sexual functioning in depressed patients taking SSRIs (Landen et al., 1999), it was hypothesized that addition of a 5-HT_{1A} receptor partial agonist to SSRI treatment would mitigate SSRI-associated sexual side effects. The pre-switch (subchronic, chronic) and post-switch results of the current study were consistent with this hypothesis, although the results with vilazodone are perhaps more persuasive than those with paroxetine + buspirone (especially after chronic treatment).

Several mechanisms may be involved in SSRI-induced sexual dysfunction. First, SSRIs such as paroxetine lead to chronic elevation of extracellular 5-HT, which increases inhibitory tone on sexual behaviors (Snoeren et al., 2014) and activates negative feedback mechanisms that reduce the tone of 5-HT neuronal activity via

various inhibitory autoreceptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{5A}) located in the raphe nuclei (Barnes and Sharp, 1999; Chan et al., 2008; Snoeren et al., 2014). 5-HT_{1A} autoreceptors have been shown to desensitize following chronic pharmacological elevation (Le Poul et al., 1995; Li et al., 1997) and gene-mediated (5-HT_T knockout rat) elevation (Chan et al., 2011) of extracellular 5-HT levels, which may partially dampen the feedback mechanism. Second, neurochemical adaptations related to postsynaptic 5-HT heteroreceptors (5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors) may also play a role in sexual function (Clayton et al., 2013a; Olivier et al., 2011). These heteroreceptors are located on GABAergic and glutamatergic cell bodies in brain areas that are involved in sexual behaviors (eg, hippocampus, septum, amygdala, hypothalamus, and entorhinal cortex), but the functions of these inhibitory and excitatory systems, respectively, on sexual behavior are not well understood (Sharp et al., 2007). Finally, sexual behavior may also be regulated by interactions between the 5-HT system and other systems that involve dopamine, noradrenaline, or oxytocin (Bijlsma et al., 2014; Rosen et al., 1999; Silverstone et al., 2012; Snoeren, 2015; Snoeren et al., 2014).

The generally comparable effects of vilazodone and paroxetine + buspirone on sexual behavior that were seen in this study may be due to their activity at both presynaptic 5-HT_{1A} autoreceptors (Ashby et al., 2013; Wong et al., 2007) and postsynaptic 5-HT_{1A} heteroreceptors (Hughes et al., 2005; Wong et al., 2007). 5-HT_{1A} receptor partial agonists stimulate inhibitory autoreceptors in the raphe nuclei, which decrease extracellular 5-HT release globally and thereby reduce inhibitory tone on sexual behavior. 5-HT_{1A} receptor partial agonists also directly stimulate postsynaptic 5-HT_{1A} heteroreceptors in brain regions that are involved in sexual behaviors (Blier and Ward, 2003; Snoeren et al., 2014); moreover, these heteroreceptors may play a role in negative feedback loops that inhibit 5-HT transmission (Casanovas et al., 1999; Hajós et al., 1999; Snoeren et al., 2014).

Although both buspirone and vilazodone are partial 5-HT_{1A} receptor agonists, buspirone is also a dopamine D2 receptor antagonist; additionally, buspirone has an active metabolite, 6-hydroxybuspirone, that may affect its 5-HT_{1A} receptor occupancy (Wong et al., 2007). It is important to note, however, that differences in 5-HT_{1A} occupancy between vilazodone and buspirone remain unclear since it is a challenge to demonstrate vilazodone's *in vivo* 5-HT_{1A} binding affinity due to competition with the endogenous ligand (5-HT) (van Amsterdam and Seyfried, 2014). However, in a small clinical study of healthy volunteers, positron-emission tomography scans showed preferential occupancy for the presynaptic versus the postsynaptic 5-HT_{1A} receptor with vilazodone but not with buspirone (Rabiner et al., 2000). Further research would be needed to better understand the differential effects of buspirone and vilazodone on human sexual functioning.

In summary, daily vilazodone treatment was not associated with sexual dysfunction in male rats, and switching to daily vilazodone treatment for 1 week normalized sexual function in rats that had previously exhibited paroxetine-induced sexual dysfunction. Vilazodone treatment may not result in sexual dysfunction in male rats due to its molecular actions as both an SSRI and 5-HT_{1A} receptor partial agonist; any effects on male rat sexual behaviors were found to be less severe than the coadministration of paroxetine + buspirone. In addition, switching to vilazodone treatment was more effective than the addition of buspirone in normalizing SSRI-induced sexual side effects, which may have clinical implications. Combination therapy of SSRIs with 5-HT_{1A} agonists and partial agonists has been shown to improve SSRI-related sexual dysfunction (Clayton and Montejó, 2006; Landen et al., 1999) and is therefore a common strategy to manage treatment in MDD patients experiencing sexual side effects (Rizvi and

Kennedy, 2013). Placebo- and active-controlled trials in patients with MDD (Clayton et al., 2013b, 2015) and placebo-controlled trials in generalized anxiety disorder (Clayton et al., 2016) have shown that vilazodone monotherapy is not associated with treatment-emergent sexual side effects. From a clinical standpoint, the relative benefits of an adjunctive versus montherapeutic approach may need to be considered when treating patients who require serotonergic medications.

Role of funding source

Funding for this study was provided by Forest Laboratories, Inc., an Allergan affiliate.

Contributors

The study was designed by R. Oosting, J. Chan, and B. Olivier in consultation with P. Banerjee. Experiments were conducted by J. Chan and R. Oosting. All authors contributed to the interpretation of results and drafting of the manuscript. The final manuscript was approved for submission by all authors.

Potential conflicts of interest

Other than support for this study, R. Oosting, J. Chan, and B. Olivier have no potential conflicts of interest to disclose. P. Banerjee is a full-time employee of Forest Research Institute (Jersey City, NJ, USA), an Allergan affiliate.

Acknowledgment

Writing and editorial assistance was provided by Jonathan Kelley and Adam Ruth, former employees of Prescott Medical Communications Group (Chicago, IL, USA), with support from Forest Research Institute, an Allergan affiliate.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.neuropharm.2016.03.045>.

References

- Adamec, R., Bartoszyk, G.D., Burton, P., 2004. Effects of systemic injections of vilazodone, a selective serotonin reuptake inhibitor and serotonin 1A receptor agonist, on anxiety induced by predator stress in rats. *Eur. J. Pharmacol.* 504, 65–77.
- Arnone, M., Baroni, M., Gai, J., Guzzi, U., Desclaux, M., Keane, P., LeFur, G., Soubrié, P., 1995. Effect of SR 59026A, a new 5-HT_{1A} receptor agonist, on sexual activity in male rats. *Behav. Pharmacol.* 276–282.
- Ashby Jr., C.R., Kehne, J.H., Bartoszyk, G.D., Renda, M.J., Athanasiou, M., Pierz, K.A., Seyfried, C.A., 2013. Electrophysiological evidence for rapid 5-HT_{1A} autoreceptor inhibition by vilazodone, a 5-HT_{1A} receptor partial agonist and 5-HT reuptake inhibitor. *Eur. J. Pharmacol.* 714, 359–365.
- Ashton, A.K., Jamerson, B.D., L. Weinstein, W., Wagoner, C., 2005. Antidepressant-related adverse effects impacting treatment compliance: results of a patient survey. *Curr. Ther. Res. Clin. Exp.* 66, 96–106.
- Barnes, N.M., Sharp, T., 1999. A review of central 5-HT receptors and their function. *Neuropharmacology* 38, 1083–1152.
- Bijlsma, E.Y., Chan, J.S., Olivier, B., Veening, J.G., Millan, M.J., Waldinger, M.D., Oosting, R.S., 2014. Sexual side effects of serotonergic antidepressants: mediated by inhibition of serotonin on central dopamine release? *Pharmacol. Biochem. Behav.* 121, 88–101.
- Blier, P., Ward, N.M., 2003. Is there a role for 5-HT_{1A} agonists in the treatment of depression? *Biol. Psychiatry* 53, 193–203.
- Bromet, E., Andrade, L.H., Hwang, I., Sampson, N.A., Alonso, J., De Girolamo, G., De Graaf, R., Demyttenaere, K., Hu, C., Iwata, N., 2011. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med.* 9, 90.
- Casanovas, J.M., Hervás, I., Artigas, F., 1999. Postsynaptic 5-HT_{1A} receptors control 5-HT release in the rat medial prefrontal cortex. *Neuroreport* 10, 1441–1445.
- Chan, J.S., Olivier, B., de Jong, T.R., Snoeren, E.M., Koopman, E., van Hasselt, F.N., Limpens, J.H., Kas, M.J., Waldinger, M.D., Oosting, R.S., 2008. Translational research into sexual disorders: pharmacology and genomics. *Eur. J. Pharmacol.* 585, 426–435.
- Chan, J.S., Snoeren, E.M., Cuppen, E., Waldinger, M.D., Olivier, B., Oosting, R.S., 2011. The serotonin transporter plays an important role in male sexual behavior: a study in serotonin transporter knockout rats. *J. Sex. Med.* 8, 97–108.
- Chan, J.S., Waldinger, M.D., Olivier, B., Oosting, R.S., 2010. Drug-induced sexual dysfunction in rats. *Curr. Protoc. Neurosci. Chapter 9, Unit 9.34*.
- Clayton, A.H., Durgam, S., Tang, X., Chen, C., Ruth, A., Gommoll, C., 2016. Characterizing sexual function in patients with generalized anxiety disorder: a pooled analysis of 3 vilazodone studies. *Neuropsychiatr. Dis. Treat.* (in press).
- Clayton, A.H., Gommoll, C., Chen, D., Nunez, R., Mathews, M., 2015. Sexual dysfunction during treatment of major depressive disorder with vilazodone, citalopram, or placebo: results from a phase IV clinical trial. *Int. Clin. Psychopharmacol.* 30, 216–223.
- Clayton, A.H., Kennedy, S.H., Edwards, J.B., Gallipoli, S., Reed, C.R., 2013a. The effect of vilazodone on sexual function during the treatment of major depressive disorder. *J. Sex. Med.* 10, 2465–2476.
- Clayton, A.H., Kennedy, S.H., Edwards, J.B., Gallipoli, S., Reed, C.R., 2013b. The effect of vilazodone on sexual function during the treatment of major depressive disorder. *J. Sex. Med.* 10, 2465–2476.
- Clayton, A.H., Montejo, A.L., 2006. Major depressive disorder, antidepressants, and sexual dysfunction. *J. Clin. Psychiatry* 67 (Suppl. 6), 33–37.
- De Jong, T., Pattij, T., Veening, J., Dederen, P., Waldinger, M., Cools, A., Olivier, B., 2005. Effects of chronic paroxetine pretreatment on (±)-8-hydroxy-2-(di-n-propyl-amino) tetralin induced c-fos expression following sexual behavior. *Neuroscience* 134, 1351–1361.
- Hajós, M., Hajós-Korcsok, É., Sharp, T., 1999. Role of the medial prefrontal cortex in 5-HT_{1A} receptor-induced inhibition of 5-HT neuronal activity in the rat. *Br. J. Pharmacol.* 126, 1741–1750.
- Hu, X.H., Bull, S.A., Hunkeler, E.M., Ming, E., Lee, J.Y., Fireman, B., Markson, L.E., 2004. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *J. Clin. Psychiatry* 65, 959–965.
- Hughes, Z.A., Starr, K.R., Langmead, C.J., Hill, M., Bartoszyk, G.D., Hagan, J.J., Middlemiss, D.N., Dawson, L.A., 2005. Neurochemical evaluation of the novel 5-HT_{1A} receptor partial agonist/serotonin reuptake inhibitor, vilazodone. *Eur. J. Pharmacol.* 510, 49–57.
- Kennedy, S.H., Rizvi, S., 2009. Sexual dysfunction, depression, and the impact of antidepressants. *J. Clin. Psychopharmacol.* 29, 157–164.
- Landen, M., Eriksson, E., Agren, H., Fahlen, T., 1999. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J. Clin. Psychopharmacol.* 19, 268–271.
- Le Poul, E., Laaris, N., Doucet, E., Laporte, A.-M., Hamon, M., Lanfumey, L., 1995. Early desensitization of somato-dendritic 5-HT_{1A} autoreceptors in rats treated with fluoxetine or paroxetine. *Naunyn Schmiedeb. Arch. Pharmacol.* 352, 141–148.
- Li, Q., Muma, N., Battaglia, G., Van de Kar, L., 1997. A desensitization of hypothalamic 5-HT_{1A} receptors by repeated injections of paroxetine: reduction in the levels of G(i) and G(o) proteins and neuroendocrine responses, but not in the density of 5-HT_{1A} receptors. *J. Pharmacol. Exp. Ther.* 282, 1581–1590.
- Lindsley, C.W., 2012. The top prescription drugs of 2011 in the United States: antipsychotics and antidepressants once again lead CNS therapeutics. *ACS Chem. Neurosci.* 3, 630–631.
- Olivier, B., Chan, J.S., Snoeren, E.M., Olivier, J.D., Veening, J.G., Vinkers, C.H., Waldinger, M.D., Oosting, R.S., 2011. Differences in sexual behaviour in male and female rodents: role of serotonin. *Curr. Top. Behav. Neurosci.* 8, 15–36.
- Oosting, R.S., Chan, J.S., Olivier, B., Banerjee, P., Choi, Y.K., Tarazi, F., 2016. Differential effects of vilazodone versus citalopram and paroxetine on sexual dysfunction and serotonin transporter and receptors in male rats. *Psychopharmacology* 233, 1025–1034.
- Page, M.E., Cryan, J.F., Sullivan, A., Dalvi, A., Saucy, B., Manning, D.R., Lucki, I., 2002. Behavioral and neurochemical effects of 5-[4-(5-cyano-3-indolyl)-butyl]-butyl]-1-piperazinyl]-benzofuran-2-carboxamide (EMD 68843): a combined selective inhibitor of serotonin reuptake and 5-hydroxytryptamine_{1A} receptor partial agonist. *J. Pharmacol. Exp. Ther.* 302, 1220–1227.
- Pattij, T., de Jong, T.R., Uitterdijk, A., Waldinger, M.D., Veening, J.G., Cools, A.R., van der Graaf, P.H., Olivier, B., 2005. Individual differences in male rat ejaculatory behaviour: searching for models to study ejaculation disorders. *Eur. J. Neurosci.* 22, 724–734.
- Rabiner, E.A., Gunn, R.N., Wilkins, M.R., Sargent, P.A., Mocaer, E., Sedman, E., Cowen, P.J., Grasby, P.M., 2000. Drug action at the 5-HT_{1A} receptor in vivo: autoreceptor and postsynaptic receptor occupancy examined with PET and [carbonyl-11 C] WAY-100635. *Nucl. Med. Biol.* 27, 509–513.
- Rizvi, S.J., Kennedy, S.H., 2013. Management strategies for SSRI-induced sexual dysfunction. *J. Psychiatry Neurosci.* 38, E27–E28.
- Rosen, R.C., Lane, R.M., Menza, M., 1999. Effects of SSRIs on sexual function: a critical review. *J. Clin. Psychopharmacol.* 19, 67–85.
- Serretti, A., Chiesa, A., 2009. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. *J. Clin. Psychopharmacol.* 29, 259–266.
- Sharp, T., Boothman, L., Raley, J., Quérée, P., 2007. Important messages in the 'post': recent discoveries in 5-HT neuron feedback control. *Trends Pharmacol. Sci.* 28, 629–636.
- Silverstone, P.H., Lallies, M.D., Hudson, A., 2012. Quetiapine and buspirone both elevate cortical levels of noradrenaline and dopamine in vivo, but do not have synergistic effects. *Front. Psychiatry* 3, 82.

- Snoeren, E.M., 2015. The role of adrenoceptors in the central nervous system in male and female rat sexual behavior. *Eur. J. Pharmacol.* 753, 229–245.
- Snoeren, E.M., Veening, J.G., Olivier, B., Oosting, R.S., 2014. Serotonin 1A receptors and sexual behavior in male rats: a review. *Pharmacol. Biochem. Behav.* 121, 102–114.
- van Amsterdam, C., Seyfried, C.A., 2014. Mechanism of action of the bimodal antidepressant vilazodone: evidence for serotonin1A-receptor-mediated autoaugmentation of extracellular serotonin output. *Psychopharmacology* 231, 2547–2558.
- Waldinger, M.D., van De Plas, A., Pattij, T., van Oorschot, R., Coolen, L.M., Veening, J.G., Olivier, B., 2002. The selective serotonin re-uptake inhibitors fluvoxamine and paroxetine differ in sexual inhibitory effects after chronic treatment. *Psychopharmacology* 160, 283–289.
- Waldinger, M.D., Zwinderman, A.H., Olivier, B., 2001. SSRIs and ejaculation: a double-blind, randomized, fixed-dose study with paroxetine and citalopram. *J. Clin. Psychopharmacol.* 21, 556–560.
- Wong, H., Dockens, R.C., Pajor, L., Yeola, S., Grace, J.E., Stark, A.D., Taub, R.A., Yocca, F.D., Zaczek, R.C., Li, Y.-W., 2007. 6-Hydroxybuspirone is a major active metabolite of buspirone: assessment of pharmacokinetics and 5-hydroxytryptamine1A receptor occupancy in rats. *Drug Metab. Dispos.* 35, 1387–1392.